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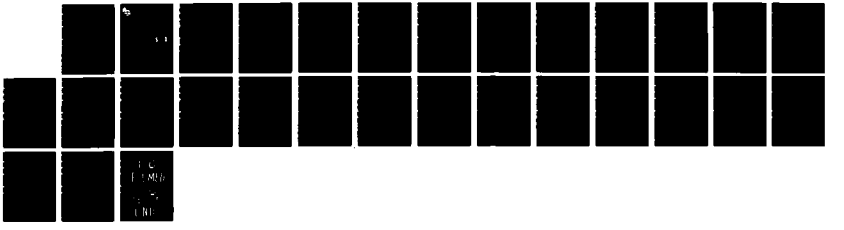

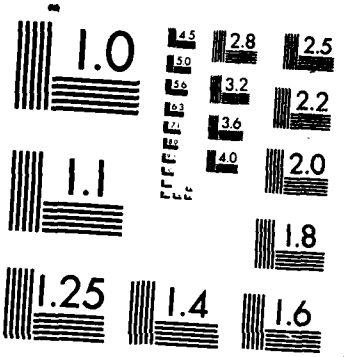

INSTITUTE REPORT NO. 211

ACUTE DERMAL TOXICITY OF BALLPOWDER IN RABBITS

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and
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DIVISION OF COMPARATIVE MEDICINE
AND TOXICOLOGY

JANUARY 1986

Toxicology Series 120

LETTERMAN ARMY INSTITUTE OF RESEARCH
PRESIDIO OF SAN FRANCISCO, CALIFORNIA 94129

Acute Dermal Toxicity of Ballpowder in Rabbits--Ryabik et al
Toxicology Series 120

In conducting the research described in this report, the investigation adhered to the "Guide for the Care and Use of Laboratory Animals," as promulgated by the Committee on Revision of the Guide for Laboratory Animal Facilities and Care, Institute of Laboratory Animal Resources, National Research Council.

This material has been reviewed by Letterman Army Institute of Research and there is no objection to its presentation and/or publication. The opinions or assertions contained herein are the private views of the author(s) and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense. *(AR 360-5)*

Edwin S. Beatrice 15 Jan 86

(Signature and date)

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Ballpowder, Acute Dermal Toxicity, Rabbit, Mammalian Toxicology

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The acute dermal toxicity of ballpowder was evaluated in rabbits by topical application to skin sites with semi-occlusive covering for 24 hours. There were no compound related deaths or clinical signs observed at a limit dose of 2 g/kg during the study. There were no dermal effects observed in any of the rabbits which could be attributed to ballpowder.

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ABSTRACT

The acute dermal toxicity of ballpowder was evaluated in New Zealand White rabbits following a 24-hour exposure period. There were no compound related deaths or clinical signs observed at a limit dose of 2 g/kg during this study. There were no dermal effects observed in any of the rabbits which could be attributed to ballpowder.

KEY WORDS: Ballpowder, Acute Dermal Toxicity, Rabbit, Mammalian Toxicology

PREFACE

TYPE REPORT: Acute Dermal Toxicity GLP Report

TESTING FACILITY: U.S. Army Medical Research and Development Command
Letterman Army Institute of Research
Presidio of San Francisco, CA 94129-6800

SPONSOR: US Army Medical Research and Development Command
US Army Medical Bioengineering Research
and Development Laboratory
Fort Detrick, MD 21701-5010
Project Officer: Gunda Reddy, PhD

PROJECT: Nitrocellulose-Nitroguanidine Project
3E162720A835
WU 180, APC TL09

GLP STUDY NO.: 84036

STUDY DIRECTOR: Don W. Korte, Jr, PhD, MAJ MSC

PRINCIPAL INVESTIGATOR: Carolyn M. Lewis, MS

CO-PRINCIPAL INVESTIGATOR: John R.G. Ryabik, BS, SP4

PATHOLOGIST: Paul W. Mellick, DVM, PhD, COL VC

REPORT AND DATA MANAGEMENT: A copy of the final report, study protocols, raw data, retired SOPs, and an aliquot of the test compound will be retained in the LAIR Archives.

TEST SUBSTANCE: Ballpowder

INCLUSIVE STUDY DATES: 24 Jan - 26 Feb 85

OBJECTIVE: The objective of the study was to evaluate the acute dermal toxicity of ballpowder in male and female New Zealand White rabbits.

ACKNOWLEDGMENT

SP4 James Fischer, PFC Scott Schwebe, and Ms. Charlotte Speckman were responsible for animal husbandry. CPT Earl Morgan served as Project Coordinator for the Nitrocellulose-Nitroguanidine Project.

SIGNATURES OF PRINCIPAL SCIENTISTS AND MANAGERS INVOLVED IN THE STUDY

We, the undersigned, declare that GLP study number 84036 was performed under our supervision, according to the procedures described herein, and that this report is an accurate record of the results obtained.

Don W. Korte / 13MAY'85

DON W. KORTE, JR., PhD / DATE
MAJ, MS
Study Director

Carolyn M. Lewis / 13 May 85

CAROLYN LEWIS, MS / DATE
DAC
Principal Investigator

JOHN R.G. RYABIK, BS / DATE
SP4, USA
Co-Principal Investigator

Paul W. Mellick 13MAY'85

PAUL W. MELLICK, DVM, PhD / DATE
COL, VC
Pathologist

DEPARTMENT OF THE ARMY
LETTERMAN ARMY INSTITUTE OF RESEARCH
PRESIDIO OF SAN FRANCISCO, CALIFORNIA 94129

REPLY TO
ATTENTION OF:

SGRD-ULZ-QA

20 November 1985

MEMORANDUM FOR RECORD

SUBJECT: Report of GLP Compliance

1. I hereby certify that in relation to LAIR GLP Study 84036 the following inspections were made:

12 February 1985

13 February 1985

2. The report and raw data for this study were audited on 15 October 1985.

3. Routine inspections with no adverse findings are reported quarterly, thus these inspections are also included in the 29 April 1985 report to Management and the Study Director.

GARY L. DUTCHER
SSG, USA
Quality Assurance Unit

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APPENDICES

Acute Dermal Toxicity of Ballpowder in Rabbits--Ryabik et al

Nitroguanidine, a primary component of US Army triple-base propellants, is now produced in a Government-owned contractor-operated ammunition plant. The US Army Bioengineering Research and Development Laboratory (USAMBRDL), as part of its mission to evaluate the environmental and health hazards of military-unique pollutants generated by US Army munitions manufacturing facilities, conducted a review of the nitroguanidine data base and identified significant gaps in the toxicity data (1). The Toxicology Branch, LAIR, was tasked by USAMBRDL to develop a genetic and mammalian toxicity profile for nitroguanidine, related intermediates/by-products of its manufacture, and its environmental degradation products. A genetic and acute mammalian toxicity profile of ballpowder, a fielded nitrocellulose-based propellant (Cartiridge 5.56 mm, Ball, M193) was also requested as a baseline against which future formulations will be compared.

Objective of Study

The objective of this study was to determine the acute dermal toxicity potential of ballpowder in male and female New Zealand White rabbits.

MATERIALS AND CONDITIONS

Test Substance

Product name: WC 844 Double-base Spheroidal Propellant

Code number: LAIR Code No. TA045

Physical state: Solid

Source: Badger Army Ammunition Plant
Baraboo, WI 53913

Other test substance information is presented in Appendix A.

Vehicle

The vehicle was sterile saline (0.9% sodium chloride for injection, USP, Travenol Laboratories, Inc, Deerfield, IL 60015, Lot No 7C950X0, Expiration Date - October 1985).

Animal Data

Five male and five female young adult New Zealand White rabbits (Oryctolagus cuniculus) were obtained from Elkhorn Rabbitry, Watsonville, CA 95076, for this study. They were identified individually by ear tattoos with numbers ranging from 85F032 to 85F036 (inclusive) for the females and from 85F040 to 85F044 (inclusive) for the males. The animal weights ranged from 2745 to 3125 g on receipt and from 2815 to 3272 g at dosing.

Husbandry

The rabbits were housed individually in stainless steel, wire mesh bottom, battery-type cages with automatically flushing dumptanks. Water was provided ad libitum by automatic lick dispensers connected to a central line. The rabbits were fed approximately 150 g of Purina Certified Rabbit Chow No 5322 (Ralston Purina Company, St Louis, MO 63164, Lot Nos: OCT05842A, NOV15842A and NOV15842B) daily. The animal room temperature was maintained between 17 and 20°C and the relative humidity between 40% and 70% except during room cleaning (spikes up to 79%, lasting 15 to 30 minutes). The photoperiod was 12 hours of light per day.

METHODS

This study was conducted in accordance with Environmental Protection Agency Guidelines (2) and Toxicology Branch Standard Operating Procedures (3).

Acclimation and Group Assignment

The rabbits were quarantined by the Animal Resources Group, LAIR, for two weeks before being certified healthy by a staff veterinarian. During quarantine they were given sulfaquinoline (3.2 ml/326 ml water bottle ad libitum for seven days) for coccidial prophylaxis and one application of Canex®/mineral oil (Pitman-Moore, Inc., Washington Crossing, NJ 08560) for earmite prevention. After being certified healthy, the rabbits were moved into a Toxicology Group animal room for the remainder of the study. The hair on the exposure site was clipped 4 days before dosing. The exposure site was clipped a second time 24 hours before dosing.

No randomization for group assignment was necessary as there was only one dose level for each sex.

Dose Levels

A limit test was conducted in which male and female rabbits were assigned to a test group receiving 2 g/kg of ballpowder.

Test Procedures

The applications sites on the dorsal and lateral sections of the animals (surface area approximately 300 cm2) were close-clipped with electric clippers (Oster® Model A5, Size 40 blade, Sunbeam Corp, Milwaukee, WI 53217) 24 hours before applying the test compound. The compound was evenly distributed over the surface of an 8 x 8-inch (20.3 x 20.3-cm) piece of gauze moistened with isotonic saline, then taped to the application site on the animal with hypoallergenic tape (Durapore® Surgical Tape, 3M Corp, St Paul, MN 55144). The trunk of the animal was then wrapped with Vetrap® bandaging tape (Animal Care products, 3M Corp, St Paul, MN 55144) to hold the compound in place and prevent the animal from ingesting the compound. The Vetrap® was anchored in place cranially and caudally by strips of Conform® tape (Kendall Co., Boston, MA 02101). The wrappings were left in place for 24 hours. No restraint of the animals was used except during the wrapping procedure. When the wrappings were removed the exposed area was wiped with a piece of gauze moistened with saline to remove any remaining test compound.

Observations

Clinical observations were recorded 1, 2, and 4 hours after dosing and daily for the remainder of the study. A second "walk through" observation was performed daily with only significant observations recorded. If dermal reactions were observed, they were recorded according to type, severity, and percent area exposed. Severity was defined as slight, mild, moderate, and severe. Area was defined as less than 5%, 5 to 10%, 10 to 25%, 25 to 50% and greater than 50% of exposed area. Percent area exposed was determined by visual approximation. Body weights were recorded once a week during the course of the study.

Necropsy

Animals that died during the study were submitted for necropsy. Those which survived the 14-day study period were submitted for necropsy immediately after being given an overdose of sodium pentobarbital and sacrificed by exsanguination from the severed axillary vessels. Skin was taken from the exposed area and examined microscopically.

Duration of Study

The study period was 14 days with a 19-day quarantine/acclimation period. Appendix B contains a listing of major study events.

Changes/Deviations

The protocol stated that ballpowder would be moistened with isotonic saline to make a paste. Since ballpowder is in the form of small spheroidal pellets, it did not lend itself to the formation of a paste. Rather, ballpowder was sprinkled evenly over the surface of the prescribed pieces of gauze moistened with isotomic saline and applied. The protocol also stated that the rabbits would be fed 150 g of Purina Certified Rabbit Chow No 5322 daily. This value is an approximation since the chow is measured volumetarically. One cup of the chow (the volume given a rabbit each day) weighs approximately 150 g. These changes/deviations did not affect the outcome of the study.

Raw Data and Final Report Storage

A copy of the final report, study protocols, raw data, SOPs, and an aliquot of the test compound will be retained in the LAIR archives.

RESULTS

Clinical Observations

Observations consisted of two major categories, systemic and dermal. No systemic signs attributable to the compound were observed in any of the animals. The only clinical sign observed during the study was slight diarrhea in four of the female and one of the male rabbits.

Equivocal signs of erythema were observed initially after removal of wrappings (Table C-1 and Table C-2, Appendix C).

A summary of the body weights during the quarantine and study period appear in Table C-3 (Appendix C).

Gross Pathological Observations

There were no gross or microscopic findings in these rabbits that could be attributed to dermal exposure to ballpowder at the 2 g/kg dose level (Appendix D).

DISCUSSION

Ballpowder produced no mortality in rabbits exposed to a limit dose of 2 g/kg. The only clinical sign observed during the study was diarrhea in four of the female and one of the male rabbits. The diarrhea occurred shortly after dosing and could be attributed to the stress of handling and dosing. Mild erythema was observed initially after removal of the wrappings in four of the ten dosed rabbits. Three of the four rabbits had less than 5% of the exposed area affected and the other rabbit had between 5% and 10% of the exposed area affected. The pattern of the erythema suggested that it was due to the wrappings procedure. The pathology report revealed no lesions attributed to the test compound. This finding was not only consistent with the observation that significant quantities of test compound remained on the back after 24 hours but also that little of the test compound was absorbed during the exposure period. Absorption of ballpowder was probably impeded due to its physical characteristics as well as its insolubility in the saline vehicle utilized. Ballpowder is insoluble in water, slightly soluble in DMSO, and soluble in acetone, ethyl acetate, and other organic solvents (4).

CONCLUSION

A limit dose of 2 g/kg of ballpowder was not lethal following dermal exposure for 24 hours, and produced no compound related clinical signs or dermal effects during the 14-day observation period. Ballpowder possesses a minimal potential for acute dermal toxicity.

REFERENCES

1. Kenyon, KF. A data base assessment of environmental fate aspects of nitroguanidine. Frederick, Maryland: US Army Meical Bioengineering Research and Development Laboratory, 1982; DTIC No AD A125591.

2. Environmental Protection Agency. Office of Pesticides and Toxic Substances, Office of Toxic Substances (Ts-792). Acute exposure, dermal toxicity. In: Health effects test guidelines. Washington, DC: Environmental Protection Agency, November 1984; EPA 560/6-82-001.

3. Acute dermal toxicity study. LAIR Standard Operating Procedure OP-STX-30, Letterman Army Institute of Research, Presidio of San Francisco, CA. 18 May 1984.

4. U.S. Army Armament, Munitions and Chemical Command. Military explosives. Washington, D.C.: Headquarters, Department of the Army, September, 1984; DA Technical Manual TM9-1300-214: 8-2.

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Appendices

PROPELLANT DESCRIPTION SHEET

REPORTS CONTROL SYMBOL
EXEMPT - PARA 7-2a AR 335-15

TO	FROM	DATE
	Badger Army Ammunition Plant Baraboo, Wisconsin 53913	10 August 1984

DA LOT NUMBER 50/50 blend of lots BAJ-47670 and BAJ-47671	COMPOSITION NUMBER WC 844 for Cartridge 5.56 mm, BALL, M193
MFG AT Badger Army Ammunition Plant	PACKED AMOUNT LB
CONTRACT NUMBER DAAA09-73-C-0004	SPECIFICATION NUMBER MIL-P-3984E w/Amendment 4 and Drawing No. C10542743 Rev. C

NITROCELLULOSE

ACCEPTED BLEND NUMBERS	NITROGEN CONTENT	KI STARCH(65.5°C)	STABILITY (134.5°C)
Nitrocellulose (NC) extracted from excessed Single Base Propellant.	MAX %	MIN	MIN
	MIN %	MIN	MIN
	AVG %	MIN	MIN
NC complied with MIL-N-244A			EXPLOSION HR

MANUFACTURE OF PROPELLANT

_____POUNDS SOLVENT PER POUND NC/DRY WEIGHT INGREDIENTS CONSISTING OF _____ POUNDS ALCOHOL AND _____ POUNDS _____ PER 100 POUNDS SOLVENT. PERCENTAGE REMIX TO WHOLE_____.

TEMPERATURE FROM	TEMPERATURE TO	PROCESS-SOLVENT RECOVERY AND DRYING	TIME DAYS	TIME HOURS

PROPELLANT COMPOSITION / TESTS OF FINISHED PROPELLANT / STABILITY AND PHYSICAL TESTS

CONSTITUENT	% FORMULA	% TOLERANCE	% MEASURED		FORMULA	ACTUAL
Nitroglycerin			10.235	HEAT TEST 120°	Min 60 min.	65 min.*
Dinitrotoluene			0.685	No Explosion (HRS)	Min 5	5+*
Diphenylamine			1.105	FORM OF PROPELLANT		
Dibutylphthalate			5.255	Dust&Foreign Mat.		0.02
Nitrocellulose			83.23	Graphite		0.075
Total Volatiles			1.045	Grav. Densit;		1.008
Moisture and Volatiles			0.895	Nitrogen		13.075
Residual Solvent			0.49			
Calcium Carbonate			0.09			
Sodium Sulfate			0.12			

CLOSED BOMB	LOT NUMBER	TEMP °F	RELATIVE QUICKNESS	RELATIVE FORCE
TEST				
STANDARD			100.00%	100.00%

PROPELLANT DIMENSIONS (INCHES)	SPEC	DIE	FINISHED	MEAN VARIATION IN % OF MEAN DIMENSIONS SPEC	MEAN VARIATION IN % OF MEAN DIMENSIONS ACTUAL
LENGTH (L)					
DIAMETER (D)					
PERF DIA (d)					
				PACKED	
				SAMPLED	
WEB DIFFERENCE /STD DEV IN % OF WEB AVERAGE				TEST FINISHED	
				OFFERED	
L:D				DESCRIPTION SHEETS FORWARDED	
D:d					

REMARKS

TYPE OF PACKING CONTAINER

REMARKS
*Tested 29 February 1984.

SIGNATURE OF CONTRACTOR'S REPRESENTATIVE	SIGNATURE OF GOVERNMENT QUALITY ASSURANCE REPRESENTATIVE

HISTORICAL LISTING OF STUDY EVENTS

DATE	EVENT
24 Jan 85	Ten rabbits arrived at LAIR. They were checked for illness and quarantined.
7 Feb 85	Ten rabbits removed from quarantine.
8 Feb 85	Rabbits examined, weighed, and clipped.
8-11 Feb 85	Rabbits checked daily for illness.
11 Feb 85	Rabbits weighed and clipped.
12 Feb 85	Ten rabbits dosed and observed 1, 2, and 4 hours after dosing.
13 Feb 85	Wrappings removed and rabbits observed for dermal irritation and clinical signs of toxicity.
13 Feb - 26 Feb 85	Rabbits observed in the morning for dermal and clinical signs. Walk-through check in afternoon.
19 Feb 85	Rabbits weighed.
26 Feb 85	Feed withheld. Ten rabbits weighed, observed, then euthanized. Gross necropsies performed. Skin from exposure site preserved for histological examination.

SUMMARY OF DERMAL SIGNS AND BODY WEIGHTS

Page

Appendix C

TABLE C-1

ACUTE DERMAL TOXICITY OF BALLPOWDER IN MALE RABBITS

SUMMARY OF DERMAL SIGNS

Male Animal No	Dermal Signs	Duration of Dermal Signs (Days)	Severity	Area[+]
85F040	None	N/A	N/A	N/A
85F041	Tape-site Rawness	1-2	A	1
85F042	Erythema*	1	A	1
85F043	Erythema*	1-2	A-B	1-2
	Tape-site Rawness	1-2	A-B	1-2
85F044	Tape-site Rawness	1-4	A-B	1

A = Slight
B = Mild
C = Moderate
D = Severe

1 = < 5%
2 = 5 to 10%
3 = 10 to 25%
4 = 25 to 50%
5 = > 50%

*Denotes equivocal signs of erythema suspected to be due to the tightness of the wrappings.

[+]Pertains to percent of exposed area exhibiting signs of dermal irritation. This value is determined by visual approximation.

TABLE C-2

ACUTE DERMAL TOXICITY OF BALLPOWDER IN FEMALE RABBITS

SUMMARY OF DERMAL SIGNS

Female Animal No	Dermal Signs	Duration of Dermal Signs (Days)	Severity	Area†
85F032	Tape-site Rawness	1-4	A-B	1
85F033	Erythema*	1-2	A-B	1
85F034	Erythema*	1	A	1
85F035	None	N/A	N/A	N/A
85F036	None	N/A	N/A	N/A

A = Slight
B = Mild
C = Moderate
D = Severe

1 = < 5%
2 = 5 to 10%
3 = 10 to 25%
4 = 25 to 50%
5 = > 50%

*Denotes equivocal signs of erythema suspected to be due to the tightness of the wrappings.

†Pertains to percent of exopsed area exhibiting signs of dermal irritation. This value is determined by visual approximation.

TABLE C-3
ACUTE DERMAL TOXICITY OF BALLPOWDER RABBITS

SUMMARY OF BODY WEIGHTS (grams)

	DAY					
	Q1	Q8	Q15	Q18	7	14
Females						
85F032	3045	3120	3131	3225	3267	3330
85F033	3125	2945	3010	3205	3245	3280
85F034	2805	2810	2852	2815	3084	3004
85F035	2985	2930	2977	3127	3156	3175
85F036	2855	2920	2981	3146	3219	3230
Mean	2963	2945	2990	3104	3194	3204
± S.E.M.	± 59	± 50	± 45	± 74	± 33	± 56
Males						
85F040	2910	2960	2998	3163	3203	3239
85F041	2875	2920	3179	3272	3339	3305
85F042	2815	2885	3040	3122	3198	3165
85F043	2915	2985	3107	3156	3263	3262
85F044	2745	2820	2944	2943	3094	3143
Mean	2852	2914	3054	3131	3219	3223
± S.E.M.	± 32	± 29	± 41	± 53	± 40	± 30

Pathology Report
GLP Study 84036

Acute Dermal Toxicity (Limit Test)
of Ballpowder (Olin WC 844 Double-Based Spheroidal Propellant)
in Male and Female New Zealand White Rabbits

1. Purpose: This study was done to determine the acute dermal toxicity of ballpowder (Olin WC 844 double-based spheroidal propellant). A limit dose of 2 g/kg was applied to the clipped unabraded skin of each rabbit. Animals were killed by exsanguination while under pentobarbitol anesthesia after a 14-day observation period. Complete gross necropsies were performed and 4 specimens of skin from the exposed area of each rabbit were processed for histologic examination. Five male and five female rabbits were treated. All survived until the end of the test.

2. Gross Necropsy Findings:

Path No.	Rabbit No.	Sex	Gross Necropsy Findings
36945	85F00032	F	No lesions
36946	85F00033	F	Otitis media, purulent, bilateral
36947	85F00034	F	Pin worms, cecum
36948	85F00035	F	Pin worms, cecum
36949	85F00036	F	No lesions
36950	85F00040	M	Pin worms, cecum
36951	85F00041	M	No lesions
36952	85F00042	M	Pin worms, cecum
36953	85F00043	M	Pin worms, cecum
36954	85F00044	M	Pin worms, cecum

3. Microscopic Findings:

Two slides each bearing 2 skin sections were prepared and examined from each animal. The only exception to this was rabbit number 85F00032 (Path No. 36945) for which 3 skin sections were submitted.

Path No.	Rabbit No.	Sex	Slide No.	Microscopic Findings Skin
36945	85F00032	F	1	No lesions
			2	No lesions
36946	85F00033	F	1	No lesions
			2	Mononuclear cell infiltration (MCI), multifocal, minimal, dermis

GLP Study 84045

Path No.	Rabbit No.	Sex	Slide No.	Microscopic Findings Skin
36947	85F00034	F	1	No lesions.
			2	MCI, minimal
36948	85F00035	F	1	MCI, minimal
			2	MCI, minimal
36949	85F00036	F	1	MCI, minimal
			2	No lesion
36950	85F00040	M	1	No lesion
			2	MCI, minimal
36951	85F00041	M	1	No lesion
			2	MCI, minimal
36952	85F00042	M	1	MCI, minimal
			2	MCI, minimal
36953	85F00043	M	1	No lesion
			2	No lesion
36954	85F00044	M	1	No lesion
			2	No lesion

4. Comments:

There were no gross or microscopic lesions in the skin of these rabbits that could be attributed to exposure to the test material. The mononuclear inflammatory infiltrates observed in the superficial dermis in 9 of 19 skin sections examined were tiny focal lesions that occupied a small fraction of the exposed area of skin. No epithelial abnormalities were observed. These small inflammatory cell foci may have been due to clipper abrasion.

Nematode parasites (pin worms) were observed in 7 of 10 animals at necropsy. These are common parasites of rabbits belonging to either Genus Dermatoxysus or Passuluris, neither of which are considered pathogenic except in very heavy infestations. Their presence would not affect the results of this dermal toxicity study.

GLP Study 84045

One of the rabbits (84F00033) had bilateral purulent otitis media. This condition is very common in rabbits from commercial sources. It is most likely due to infection by bacteria (Pasteurella spp.). This lesion is considered an incidental finding unrelated to application of the test material. The lesion would not affect the results of this dermal toxicity study.

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Diplomate, American College of
Veterinary Pathologists
COL, VC, USA
Division of Research Support

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